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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,031	03/07/2006	Maria Jose Fernandez	4258-117	6063

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INTELLECTUAL PROPERTY / TECHNOLOGY LAW
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EXAMINER	
WESTERBERG, NISSA M	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,031	FERNANDEZ ET AL.	
	Examiner	Art Unit	
	Nissa M. Westerberg	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 - 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 - 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 20, 2009 has been entered.

Response to Amendment

2. The declaration under 37 CFR 1.132 filed May 6, 2009, and in view of the amended claims filed April 20, 2009, is sufficient to overcome the rejection of claims 1 – 18 based upon Grandfils et al. (US 5,962,566).

Claim Rejections - 35 USC § 112 – 1st Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1 – 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. The application as originally filed does not provide support for the exclusion of a cholesterol compound from the method and/or nanoparticles. The passage cited by Applicant as providing support for this limitation is present in the discussion of the teachings of document US 5,962,566 as indicating that cholesterol must be included in the composition. This passage does not provide support for the exclusion of cholesterol from the compositions. Applicants do have support for the specific formulations presented in the specification, which happen to not contain cholesterol, but not for the claims as now amended.

5. Claims 1 – 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection. None of the polyoxyethylene-derived block copolymers other than those explicitly identified in the Application (e.g., poloxamers and poloxamines) meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural

information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus of polyoxyethylene-derived block copolymers encompassed by the claim, since there is no description of the structural relationship of these derived block copolymers provided in the specification and Applicant has not provided a description as to how the base monomer of polyoxyethylene may be changed while the resulting polymer remains a polyoxyethylene-derived block copolymers.

6. Claims 1 - 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of making nanoparticles presented in the specification, does not reasonably provide enablement for all methods of making nanoparticles encompassed by the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The disclosure and claims of the application have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2nd 1400 (Fed. Cir. 1988) as to undue experimentation

The factors include:

1. The nature of the invention;
2. The breadth of the claims;
3. The predictability or unpredictability of the art;
4. The amount of direction or guidance presented;
5. The presence or absence of working examples

6. The quantity of experimentation necessary;

7. The state of the prior art; and

8. The relative skill of those skilled in the art.

Each factor is address below on the basis of comparison of the disclosure, the claims and the state of the art in the assessment of undue experimentation.

1. The nature of the invention, breadth of the claims: A method of producing nanoparticles have size of less than 1 μm, and the product produced by that process are claimed. The method involves dissolving a biodegradable polymer and a polyoxyethylene-derived block copolymer (with the weight ratio ranging between 1:0.1 to 1:3) in a nonpolar organic solvent; adding with stirring the nonpolar solvent and polymer solution to a polar phase in which the biodegradable polymer has a low solubility to precipitate the polymer and form nanoparticles; eliminating the organic solvent and then isolating the particles. An active ingredient dissolved in either organic solvent or aqueous phases can be added to during or after the first step. A proviso is present excluding a cholesterol compound from the method.

2. The amount of direction or guidance presented, the presence or absence of working examples; quantity of experimentation necessary, the state of the prior art, and the relative skill of those skilled in the art: The relative skill of those skilled in the art is high. In the specification, particles are prepared a polylactic co-glycolic acid (PLGA)

polymer are combined with various amounts of PLURONIC® F68, PLURONIC® L121, TETRONIC® 908, TETRONIC® 904 and resulted in the formation of particles with a size of less than 300 nm (see Example 1 - 5). These examples encompass two different polyoxyethylene-derived block copolymers with varying HLB values and one biodegradable polymer. In the declaration filed May 6, 2009 by Ana Isabel Vila Pena and Balbina Fernandez Martinez, a method was used which falls within the scope of the instant claims. In this examples, PLGA 503 and Poloxamer (no number given; poloxamer is the generic term for the block copolymer associated with the trade name PLURONIC®) in a weight ratio of 1:1, in the absence of cholesterol, did NOT result in the formation of nanoparticles as the mean particle size was about 6 microns. The inclusion of cholesterol, now excluded from the compositions and method of the instant claims, did result in the formation of the nanoparticles as the average particle size was 119 nm. Because of the similarities of the examples given in the specification and the formulation that does not result in the formation of nanoparticles, in which PLGA was used as the biodegradable polymer with a PLURONIC® polymer as the polyoxyethylene derived block copolymer in dichloromethane indicates that the full scope of the claims is not enabled. Undue experimentation would be required to determine which combination(s) of biodegradable polymers and polyoxyethylene-derived block copolymers in what weight ratios within the limits specified by Applicant do result in the formation of nanoparticles and those combinations of ingredients result which do not, as methods involving the same biodegradable formulation and a PLURONIC® polymer do not all results in the formation of particles as required by the instant claims.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1 – 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "the active ingredient" in line 8 of claim 1 lacks antecedent basis. It also appears that the solution added in step b) and referred to as a "polar phase" is the same phase being referred to in line 9 as the "aqueous phase". However, "aqueous phase" is a narrower term and there are polar phases which are not aqueous, such as DMSO. It also unclear what is meant by "cholesterol compound" and if compounds other than cholesterol such as the cholesterol derivatives cholesteric lipids are encompassed by this term. Please clarify.

9. Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear what steps are associated with item d) in the claim, namely if the method steps associated with the active ingredient fall under step d). In claim 19, the method consists of step a) through d). The various steps up to d) are separated using semicolons. "Isolating the particles" and the wherein clause relating to the active ingredient are not separated by a semicolon but by a comma, seeming to

indicate that both are part of step d). However, the step involving the active ingredients is either performed concurrently with step a) or after a), and the particles isolated in step d) have not been formed at step a) or just after step a). Thus, it is unclear what steps are included in claim 19 and whether or not the addition of an active ingredient concurrent with step a) or after step a) is unclear.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1 – 3, 5 – 7, 10 – 18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koll et al. (US 6,346,274) in view of Soppimath et al. (J Controlled Relase 2001).

Koll et al. discloses microparticles of a biodegradable polymer matrix and a polypeptide active ingredient (abstract; col 3, ln 56 – 67). These particles are produced by a process in which the polymers are dissolved in dichloromethane, used by Applicant as a nonpolar organic solvent, and the active ingredient EPO, an active molecule with therapeutic properties, is dissolved in an aqueous phase; the aqueous (polar) phase and the nonpolar polymer solutions are mixed using stirring to produce an emulsion (example 1, col 8, ln 13 – 31). The polymers used comprise both lactic acid and glycolic acid blocks (col 3, ln 56 – 61). The emulsion is added to another aqueous solution and then the dichloromethane phase is evaporated and the particles are isolated by suction filtration (col 8, ln 31 – 40). Additives can be included in the composition (1% to 20% by weight relative to the total amount of microparticles (col 8, ln 24 – 26). Suitable additives include the polyoxyethylene derived block co-polymers PLURONIC® F68 (MW – 8,400) and F127 (MW = 12,600; Tables 1 and 2, col 9 – 10). The prepared microparticles are

mixed with phosphate buffered saline (PBS) buffer and 0.01% TWEEN® 20, resulting in a pharmaceutical composition comprising the nanoparticles.

Koll et al. does not explicitly disclose the size of the particles produced using this process.

Soppimath et al. discloses that nanoparticles (NPs) generally vary in size from 10 to 1000 nm (p 1, col 2, ¶ 2). Nanoparticles can be prepared through a solvent evaporation method by dispersing preformed polymers such as PLGA or polycaprolactone (p 2, col 1 – 12, Section 2.1 and 2.1.1). In contrast to the process disclosed in Koll et al., the O/W water emulsion is not mixed with second aqueous solution prior to removing the organic solvent. (p 2, col 2, ¶ 1). Altering the process variables with alter the properties of the nanoparticles obtained (p 2, col 2, ¶ 1).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to prepare particles as disclosed by Koll et al. and to use a solvent evaporation process in which the organic solvent is evaporate from an O/W emulstion and to adjust the process parameters to result in particles whose size was 1000 nm or less as taught by Soppimath et al. One of ordinary skill would have been motivated to do so and reasonably would have expected success as both Koll et al. and Soppimath et al. teach the production of biodegradable nanoparticles by solvent evaporation processes. Varying the size of the particles will affect the release characteristics and the amount of drug that can be contained within the particles. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine

practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient, such as poloxamer, to add in order to best achieve the desired results. The amount of additive can influence the physical properties of the produced particles (compare PLURONIC® F127 at 0.5% and 10% in tables 1 and 2 of Koll et al.). Changes in the amount of additive would thus change the ratio of biodegradable polymer to polyoxyethylene-derived block copolymer.

The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original) For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355 If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention. In re De Lajarte, 337 F.2d 870, 143 USPQ 256 (CCPA 1964). See also Ex parte Hoffman, 12 USPQ2d 1061, 1063-64 (Bd. Pat. App. & Inter. 1989) **MPEP 2111.03** Thus, claim 18 will be interpreted as being open as no indication of the excluded steps are provided by Applicant.

Claim 19 uses the closed language of "consisting of", which could result in the exclusion of the step in which the active ingredient is added. In this interpretation of the claim, while drug particles can be used fro drug delivery and therefore would include active ingredient, for the purposes of studying the physical properties and behavior of the nanoparticles, it may be desirable to omit the active ingredient, which may be an expensive ingredient, to prepare nanoparticles for such studies. Once the process parameters have been optimized, the drug could then be included in the composition when the materials prepared will be used for drug delivery.

14. Claims 1 – 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koll et al. and Soppimath et al. as applied to claims 1 – 3, 5 – 7, 10 – 18 and 20 above, and further in view of Levy et al. (WO 96/20698).

Koll et al. and Soppimath et al. disclose a solvent evaporation process for the production of nanoparticles comprised of a biodegradable polymer such as PLGA or polycaprolactone with additives such as PLURONIC® polyoxyethylene-derived block copolymers. The PLGA or polycaprolactone is dissolved in a nonpolar organic solvent such as dichloromethane and the process parameters optimized for the desired particle size.

Neither reference discloses the use of polyanhydrides or poloxamines in the nanoparticles.

Levy et al. discloses biodegradable controlled release nanoparticles (abstract). When hydrophilic active agents are to be incorporated into the nanoparticles, the

polymer is dissolved in a solvent such as methylene chloride or chloroform (p 18, ln 8 – 11). The bioactive agent is dissolved in a semipolar organic solvent which, after being combined with the nonpolar organic solvent, is emulsified with an aqueous phase to form nanoparticles (p 18, ln 11 – 15). Among the biocompatible, biodegradable synthetic polymers which may be used to form nanoparticles are PLGA, polycaprolactone and polyanhydrides (p 7, ln 17 – 20). Poloxamers or poloxamines such as those sold under the trade name TETRONIC® 908 can be included as a synthetic polymer which is useful for modifying the surface of the particles (p 13, ln 10 – 15). These surface agents allow for targeting, enhanced sustained drug release, protection of the bioactive ingredient improve suspendability and/or preventing aggregation of the nanoparticles (p 13, ln 1 – 7).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to incorporate poloxamers into the nanoparticles taught by Koll et al. and Soppimath et al. aned/or to use a polyanhydride as the biodegradable polymer. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because various additives such as the various PLURONIC® or TETRONIC® polymers will have different effects of the surface effects of the nanoparticles. The different biodegradable polymers will degrade at different rates, allowing for differential drug release based on the inherent degradation rate of the polymer.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jake M. Vu/
Primary Examiner, Art Unit 1618

NMW